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AKERMAN SENTERFITTT				
P.O. BOX 3188				
WEST PALM BEACH, FL 33402-3188				
EXAMINER				
STAPLES, MARK				
ART UNIT		PAPER NUMBER		
1637				
NOTIFICATION DATE		DELIVERY MODE		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@akerman.com

### Office Action Summary

**Application No.**

10/516,361

**Applicant(s)**

ISLAM ET AL.

**Examiner**

MARK STAPLES

**Art Unit**

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 13 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 98-109, 117 and 119-158 is/are pending in the application.
- 4a) Of the above claim(s) 99-109, 117, 125-129, 132-134, 137-140, 144, 149, 156, and 157 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 98, 119-124, 130, 131, 135, 136, 141-143, 145-148, 150-155 and 158 is/are rejected.
- 7) ☒ Claim(s) 119, 146-148, 150, 157 and 158 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 April 2009 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (\*PTO-652)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-419)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. Applicant's amendment of claims 98, 100, 101, and 106-109, the cancellation of claims 63-97, 110-116, and 118, and submission of new claims 119-158 in the paper filed on 04/13/2009 is acknowledged. Claims 99-109 and 117 remain withdrawn.

2. Newly submitted claim 156 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claim 156 is drawn to a kit which is a non-elected invention of Group II (see Requirement for Restriction/Election mailed on 01/14/2008).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 156 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Newly submitted claims 125-129, 132-134, 137-140, 144, 149, and 157 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The claims are drawn to methods comprising steps using four or more oligonucleotide primers which are non-elected inventions. The new claims recite methods which are not in either Group I or Group II (see claims filed 10/29/2007 with

methods comprising steps using only up to three oligonucleotide primers which the recited third oligonucleotide and Requirement for Restriction/Election mailed on 01/14/2008).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 125-129, 132-134, 137-140, 144, 149, and 157 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted that Applicant's previously elected the Subgroup which is the primer pair of sequences given in SEQ ID NOs: 19 and 25 in the reply filed on 05/28/2008.

Claims 125-129, 132-134, 137-140, 144, 149, 156, and 157 are withdrawn.

Claims 98, 119-124, 130, 131, 135, 136, 141-143, 145-148, 150-155, and 158 consonant with the election of the subgroups of SEQ ID NOs: 19 and 25 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**Oath/Declaration**

4. The Oath filed on 12/22/2008 is accepted.

**Drawings**

5. The drawings filed on 04/13/2009 are accepted.

**Specification**

6. The abstract to the title is withdrawn in light of Applicant's amendment of the abstract.

**Objections and Rejections that are Moot / Withdrawn**

***Objections and Rejections of Canceled Claims are Moot / Withdrawn***

7. The objections to and rejections of canceled claims 63-97, 110-116, and 118 are moot and therefore are withdrawn.

***Claim Rejections Withdrawn - 35 USC § 103(a)***

8. The rejection of claim 98 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. as applied to claim 63, and further in view of Webb et al. (1993) and Buck et al. (1998) is withdrawn, as claim 63 has been canceled. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

The Table below is provided for discussion which follows.

## Table 1

### 100% Sequence Matches for SEQ ID Nos. 19 and 25

#### SEQ ID NO. 19

Application 10516361 and Search Result 20080724\_093709\_us-10-516-361b-19.rge.

Title: US-10-516-361B-19  
Perfect score: 20  
Sequence: 1 ggggtactacagcgccctga 20

#### RESULT 5

LEIGPAA  
LOCUS LEIGPAA 3105 bp DNA linear INV 26-APR-1993  
DEFINITION L.donovani.  
ACCESSION M60048  
VERSION M60048.1 GI:159334  
KEYWORDS glycoprotein 63.  
SOURCE Leishmania donovani  
ORGANISM Leishmania donovani  
Eukaryota; Euglenozoa; Kinetoplastida; Trypanosomatidae;  
Leishmania.  
REFERENCE 1 (bases 1 to 3105)  
AUTHORS Webb, J.R., Button, L.L. and McMaster, W.R.  
TITLE Heterogeneity of the genes encoding the major surface  
glycoprotein  
of Leishmania donovani  
JOURNAL Mol. Biochem. Parasitol. 48 (2), 173-184 (1991)  
PUBMED 1762629  
COMMENT Original source text: L.donovani DNA.  
FEATURES Location/Qualifiers  
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/mol\_type="genomic DNA"  
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VRQVQDKWKVTGMGNEICGHFKVPPAHITDGLSNTDFVMYVASVPSEGDVLAWATTQ  
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ASDAGYYSALTMAIFQDLGFYQADFSKAEEMPWGRNAGCAFLSEKCMEDGITKWPAMF  
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TYSVQVHGGSGYANCTPGLRVELSTVSSAFEEGGYITCPPYVEVCQGNVQAAKDGGNA  
AAGRRGPRAAATALLVAALLAVAL"  
ORIGIN

Query Match 100.0%; Score 20; DB 12; Length 3105;  
Best Local Similarity 100.0%; Pred. No. 6.2;  
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps  
0;

Qy 1 GGGGTACTACAGCCCTGA 20  
|||||  
Db 1114 GGGGTACTACAGCCCTGA 1133

## SEQ ID NO. 25

### From NCBI

LOCUS LEIGPAA 3105 bp DNA linear INV 26-APR-1993  
DEFINITION L.donovani.  
ACCESSION M60048  
VERSION M60048.1 GI:159334  
KEYWORDS glycoprotein 63.  
SOURCE Leishmania donovani  
ORGANISM Leishmania donovani  
Eukaryota; Euklenozoa; Kinetoplastida; Trypanosomatidae;  
Leishmania.  
REFERENCE 1 (bases 1 to 3105)  
AUTHORS Webb,J.R., Button,L.L. and McMaster,W.R.  
TITLE Heterogeneity of the genes encoding the major surface  
glycoprotein of Leishmania donovani  
JOURNAL Mol. Biochem. Parasitol. 48 (2), 173-184 (1991)  
PUBMED 1762629  
COMMENT Original source text: L.donovani DNA.  
FEATURES Location/Qualifiers  
source 1..3105

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VFS DGH PAVGVINIP AANIA SRYDQLVTRVVTHEMAHALGFSVVFRRDARILESISNV
RHKDFDVPVINSS TAVAKAREQYGC GTLEYLEME DQGGAGSAGSHIKMRNAQDEL MAP
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ORIGIN
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    61 cacaccccac tgcccacagc gcccccgcgc ctcgacagcc atgtccgtcg acagcagcag
   121 caccgcaccg caccgcagcg tcgccgcgcg cctggtcgcg ctgcgcgctg ccggcgcgcg
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   421 ctccgcctac cactgcgctc gcgtcgggca gcgtattagc acgcgcgatg gccgcttcgc
   481 catctgcacc gccgaggaca tctcaccgca cgagaagcgc gacatcctgg tcaaatacct
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   601 gtggaagggt acgggcattg gcaacgagat ctgtggccac ttcgaaggtc cgcggcgcca
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   841 tgtcgtcacc cagcagatgg gcacgcgcgt cggcttcagc gtcgtcttct tccgagacgc
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  1141 catcttcagg gacctcggct tctaccagcg gaacttcagc aaggccgagg agatgccgtg
  1201 gggccggaac gccggctcgc ctttctctag cgagaagtgc atggaggacg gcatacagaa
    
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1261 gtggccggcg atgttctgca atgagaacga ggtgactatg cgtgccaca ccggtcgtct
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Length=3105
Score = 40.1 bits (20), Expect = 8e-06
Identities = 20/20 (100%), Gaps = 0/20 (0%)
Strand=Plus/Minus

```

```

Query 1 GTCTTGAAGATGGCCATGG 20
|||||
Sbjct 1153 GTCTTGAAGATGGCCATGG 1134

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**New Objections and Rejections Necessitated by Amendment**

***Claim Objections***

9. Claim 119 is objected to because of the following informalities: recitation of "eaction" in line 9 when it appears that "reaction" is intended. Appropriate correction is required.
10. Claims 146-148, 150, and 157 are objected to. The claims do not properly indicate the trademark/trade names TEXAS RED™, CY5™, CY3™, PICOGREEN®, YO-PRO®, and/or SYBERGREEN®. They and any other trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

11. Claim 158 is objected to because of the following informalities: the claim does not end in a period. Appropriate correction is required.

***New Claim Rejections - 35 USC § 112, Second Paragraph***

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 146, 148, and 150 contain the trademark/trade name TEXAS RED™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218

USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a donor and/or acceptor FRET moiety and, accordingly, the identification/description is indefinite. This rejection can be overcome by reciting the chemical name of the donor or acceptor along with the properly indicated trademark at each occurrence, provided there is support in the originally filed application.

***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 119-124, 130, 131, 135, 136, 141, 145-148, 150-155, and 158 are rejected under 35 U.S.C. 103(a) as being unpatentable over Myakishev et al. (January 2001) as referenced to and evidenced by Nauck et al. (1999), Nazarenko et al. (2000, previously cited), and as evidenced by Becker et al. (1999) and Holland et al. (1991).

Regarding claim 119, Myakishev et al. teach improved methods of detection and/or quantification of a nucleic acid target sequence by a nucleic acid amplification reaction (entire article, especially the Title and Abstract) comprising:

(i) a first oligonucleotide sufficiently complementary to hybridize to a first nucleic acid strand of a target sequence and to act as a nucleic acid amplification primer, and a second oligonucleotide sufficiently complementary to hybridize to the complement of the said first nucleic acid strand and to act as a nucleic acid amplification primer (see Figures 1 and 2) in an appropriate reaction mixture containing the said sample and a polymerase (see 4<sup>th</sup> paragraph on p. 164) where the polymerase is Taq polymerase which is a DNA polymerase which (see the last sentence on p. 167 continued to p. 168 and noting that Nazarenko et al. teach that Taq polymerase is a DNA polymerase, as given below) , wherein the said reaction mixture is subjected to an initial denaturation followed by repeated cycles of a combination of a denaturation step and at least a selective annealing step,

(ii) the said first and the second oligonucleotide primers do not form any combination in absence of an amplification reaction, wherein the improvement comprises:

(ii) the presence of a target sequence in the sample being detected with improved sensitivity and specificity of the amplification product through the generation of a signal mainly on formation of a combination of the two primers and a combination of the two labels on the two separate primers on target amplification (entire article, especially the 1<sup>st</sup>, 3<sup>rd</sup>, and last paragraphs on p. 167 and Figure 2), and illuminating the amplification reaction mixture to measure fluorescence in a single tube (see 3<sup>rd</sup> paragraph on p. 163 and Figure 4);

(iii) determining an additional specificity of the target detection by subjecting the amplified product to a melting temperature analysis (see 4<sup>th</sup> sentence of the 2nd paragraph on p. 163).

Further regarding claim 119, Nauck et al. (as referenced by Myakishev et al.) also provide evidence that melting curve analysis was well known in the art for detection and quantification of nucleic acids (entire article especially the title).

Regarding claim 119, Myakishev et al. teach PCR cycles (see last sentence of the 3<sup>rd</sup> paragraph on p. 165) but do not specifically disclose the well known initial denaturation followed by repeated cycles of a combination of a denaturation step and at least a selective annealing step of PCR.

Regarding claims 120, 121, and 135, Myakishev et al. teach primer dimers (see the last sentence on p. 167 continued to p. 168) and teach that amplification product

varies from 7 to 157 bp of the primers in the primer dimer and teach the amplification product which is the primer dimer and thus with 0 bp difference from the primer dimer, which teachings and range also overlaps the range of 0-25 bp but does not recite that the amplification product of the target product is the size of the primer dimer.

Further regarding claims 120, 121, and 135, Myakishev et al. teach primer dimers (see the last sentence on p. 167 continued to p. 168).

Also regarding claims 120 and 121, Nauck et al. teach primer dimers and teach that amplification product is 2 bp of the two/dimer primers length (see Figure 1) which teachings and range also overlaps the range of 0-25 bp and noting instant claim 120 does not recite that the amplification product is the size of the primer dimer.

Myakishev et al. teaches a method of amplifying nucleic acids to give products of 7-25 bp more than the primer dimer. Nauck et al. teaches a method of amplifying nucleic acids to give products of 2 bp more than the primer dimer.

Myakishev et al. and Nauck et al. in combination do not teach a method of amplifying nucleic acids to give products of 0-1 more than the primer dimer which is the lower part of the claimed range of 0-25 bp more than the primer dimer.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to amplifying products of 2 and 7-25 bp more than the primer dimer as taught by Myakishev et al. since these differences in amplification product size would not be expected to greatly alter the conditions for detection. Though the effective size of a single amplification product would be the larger than the lower

part of the claimed range, this would be offset by the varying the CG content to give a detectable Tm (see 1<sup>st</sup> paragraph on p. 164 of Myakishev et al.). This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) “We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties.” Thus, an ordinary practitioner would have recognized that the conditions for detection could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of conditions for detection was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan would expect amplification products of 2 and 7-25 bp more than the primer dimer length to have nearly identical properties in the amplification of nucleic acid product of 0-1 bp more than the primer dimer length. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

Regarding claim 122, Myakishev et al. teach five primers (see last paragraph on p. 164) and teaches a first primer labeled near the 3' (the label being 11 nucleotides

near to the 3' end, see the first structure in Structure 1) and a third primer complementary to and linked to the 5' end of the first primer and labeled with fluorescein in a hairpin arrangement (again see the first structure in Structure 1 and note the complementary hybridized third primer); teach a an unlabeled second primer which can be any one of the two tailed allele primers and the reverse primer (see last paragraph on p. 164) and teach improved amplification by illuminating the amplification reaction mixture to measure fluorescence in a single tube (entire article, especially the 1<sup>st</sup>, 3<sup>rd</sup>, and last paragraphs on p. 167 and Figure 2 and see 3<sup>rd</sup> paragraph on p. 163 and Figure 4); determining an additional specificity of the target detection by subjecting the amplified product to a melting temperature analysis (see 4<sup>th</sup> sentence of the 2nd paragraph on p. 163).

Further regarding claim 122, Nauck et al. (as referenced by Myakishev et al.) also provide evidence that melting curve analysis was well known in the art for detection and quantification of nucleic acids (entire article especially the title).

Regarding claim 123, Myakishev et al. teach as noted above and teach first and second primers which are dual labeled quenched primers (see Figure 1 and noting that the Quencher and Fluorophore pair in each of first and second primer).

Regarding claim 119, Nazarenko et al. teach improved methods of detection and/or quantification of a nucleic acid target sequence by a nucleic acid amplification reaction (entire patent, specifically column 7 lines 14-21) comprising:

(i) a first oligonucleotide sufficiently complementary to hybridize to a first nucleic acid strand of a target sequence and to act as a nucleic acid amplification primer, and a second oligonucleotide sufficiently complementary to hybridize to the complement of the said first nucleic acid strand and to act as a nucleic acid amplification primer in an appropriate reaction mixture by teaching:

"The invention provides a method for detecting or measuring a product of a nucleic acid amplification reaction comprising: (a) contacting a sample comprising nucleic acids with at least two oligonucleotides, a first one of said oligonucleotides comprising a sequence complementary to a preselected target sequence that may be present in said sample, and said first one and a second of said oligonucleotides being a pair of primers adapted for use in said amplification reaction . . . " (see column 13 lines 27-34),

"In another embodiment, the donor moiety is located on a first oligonucleotide and the acceptor is located on a second oligonucleotide" (see column 16 lines 23-26),

and teach that the donor and acceptor can be MET moieties and FRET moieties which are a type of MET moieties and teach the MET/FRET distance is 10-100 Angstrom (see column 1 lines 14-16 lines 30-56) which is within the range of 10-80 Angstrom,

and teach: "The target nucleic acid can be genomic or cDNA or mRNA or synthetic, human or animal, or of a microorganism . . (see column 20 lines 3-5);

the amplification reaction mixture containing the said sample and a polymerase, where the polymerase is a DNA polymerase (see claim 95) which can be Taq polymerase (see column 25 lines 12-16), wherein the said reaction mixture is subjected to an initial denaturation followed by repeated cycles of a combination of a denaturation step and at least a selective annealing step (taught throughout the patent, see for example column 56 lines 32-38 and see Figure 5 and its description at the bottom of column 8) ,

(ii) the said first and the second oligonucleotide primers do not form any combination in absence of an amplification reaction as they are hairpin primers , wherein the improvement comprises:

(ii) the presence of a target sequence in the sample being detected with improved sensitivity and specificity of the amplification product through the generation of a signal mainly on formation of a combination of the two primers and a combination of the two labels on the two separate primers on target amplification, and illuminating the PCR amplification reaction mixture in thin walled tubes with an UV transilluminator image analysis system (see Figure 23 and its description at column 11 lines 9-15).

Regarding claim 119, Nazarenko et al. teach melting (column 42 line 49) but do not specifically teach step (iii) of determining an additional specificity of the target detection by subjecting the amplified product to a melting temperature analysis.

Regarding claims 124, 130, 131, 135, 136, 145, and 158, Nazarenko et al. teach providing a third oligonucleotide labeled with a third label moiety and teach first , second, and third oligonucleotide primers by teaching "a third nucleotide sequence of 6-30 nucleotides, wherein a nucleotide within said third nucleotide sequence is *labeled with a second moiety* [noting that this is the third label of the claims as Nazareko et al. teach that their can be a second primer with different labels as given above and where label can internal on the oligonucleotide, see claims 1-4 and Table 5] selected from the group consisting of said donor moiety and said acceptor moiety, and said second moiety is the member of said group not labeling said first nucleotide sequence, wherein

said third nucleotide sequence is sufficiently *complementary* in reverse order to said *first nucleotide sequence* for a duplex to form between said first nucleotide sequence and said third nucleotide sequence such that said first moiety and second moiety are in sufficient proximity such that, when the donor moiety is excited and emits energy, the acceptor moiety absorbs energy emitted by the donor moiety; and (d) at the 3' end of said oligonucleotide, a fourth, single-stranded nucleotide sequence of 8-40 nucleotides that comprises at its 3' end a sequence sufficiently complementary to a preselected target sequence so as to be able to prime synthesis by a nucleic acid polymerase of a nucleotide sequence complementary to a nucleic acid strand comprising said target sequence; wherein when said duplex is not formed, said first moiety and said second moiety are separated by a distance that prevents molecular energy transfer between said first and second moiety" (emphasis by Examiner, see column 20 lines 21-66, and see Figure 6 and see column 8 lines 60-65). Furthermore, Nazarenko et al. teach that multiple primers can be used in amplification and that each primer can be labeled with different fluorophores and/or different quenchers (see Table 1 for a list of FRET pairs and see column 17 lines 46-67). Furthermore, Nazarenko et al. teach that primers may be provided in semi-nested amplification which is a type of nested amplification (see column 4 lines 9-16). Even further, Becker et al. teach a third oligonucleotide can be used to nest between FRET primers (see Real-time PCR on p. 2563 and referencing Holland et al.).

Further regarding claims 124, 130, 131, 135, and 136, Nazarenko et al. Nazarenko et al. teach as noted above and teach amplification teach:

a primer labeled near the 3' end (see R of Fig. 7),  
an unlabeled primer (see F of Fig. 7),  
a third labeled oligonucleotide (see P of Fig. 7),  
where the labeled primer is incorporated into the sequence (see Fig. 7) and  
where the labels are MET/FRET donor and acceptor and come within the MET distance  
on the target nucleic acid (as given above and see Fig. 7).

Regarding claim 141, Nazarenko et al. teach multiplexing of targets and labels  
(see column 36 lines 3-9).

Regarding claims 146-148, 150, and 157, Nazarenko et al. teach donors and  
acceptors of fluorescein, DABCYL (see column 3 lines 3-17), and ethidium bromide  
(see column 10 line 30 and claim 37) which inherently is an intercalator and teach  
rhodamine (claim 23), carboxy fluorescein (claim 25), Malachite green (claim 40), and  
TEXAS RED® acceptor (claim 41).

Regarding claim 151, Nazarenko et al. teach biotin and avidin (see column 19  
lines 50-57).

Regarding claim 152, Nazarenko et al. teach adding polymerase, reaction buffer,  
deoxy nucleoside triphosphates (dNTPs) in addition to the effective amounts of the  
amplification primers to the samples, cycling the sample between at least a denaturation  
temperature and an elongation temperature, exciting the reaction mixture with the donor  
exciting radiation or light, measuring the emission of the acceptor MET moiety (see  
column 35 lines 46 to column 36 line 61 and see column 38 lines 16-26).

Regarding claim 153, Nazarenko et al. teach a first hairpin oligonucleotide 10 -40 bases line with a stem structure which are DNA (see Figure 1A and 1B and column 23 lines 1-11 and Figure 26) and where the target sequence can be RNA (see column 14 line 33).

Regarding claim 154, Nazarenko et al. teach PCR (see Figure 23 and its description at column 11 lines 9-15).

Regarding claim 155, Nazarenko et al. where the target nucleic acid sequence is an amplification product of the infectious disease agent which is Chlamydia (see Table 3).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the PCR amplification methods of Myakishev et al. as referenced to and evidenced by Nauck et al. by performing PCR amplification cycles with denaturation and annealing as suggested by Nazarenko et al. with a reasonable expectation of success. The motivation to do so is provided by Nazarenko et al. who teach that the cycling in PCR comprises denaturation and annealing (see column 56 line 31-38). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

#### Lengths of Primers/Probes and Donor-Acceptor Distance

Myakisheve et al. teach primers of approximately 18 -23 bases in length and teach primer tails of approximately 18 bases in length (see Table 1)

Nauck et al. teach 18 base length primers and probes (see *Design of Primers and Fluorogenic probes* on p. 1142).

Nazarenko et al. teach primers can vary in length from 8-40 bases (see column 8 lines 36-40), that placement of fluorophore donors and quencher acceptors can vary, and that distance between the fluorophore and quencher can vary (entire patent, especially column 8 lines 36-56 and column 20 lines 21-56).

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use primers and probes of different sizes such as used by the applicant or in the range of the primers and probes as used by Myakisheva et al., Nauck et al., and Nazarenko et al. since these differences in primer and probe size and donor-acceptor distance would not be expected to greatly alter the conditions for amplification. Though the size of a specific primer or a specific probe may be different, this would be offset by the larger absolute amounts amplification reagents such as the base composition and specificity of the primers and probes. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the primer/probe size and donor-acceptor distance could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of primer/probe size and donor-acceptor distance other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan would expect the claimed primer and probe sizes to have nearly identical properties in the amplification of nucleic acids. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

17. Claim 98 is rejected under 35 U.S.C. 103(a) as being unpatentable over Myakishev et al., Nauck et al., Nazarenko et al., Becker et al., and Holland et al. as applied to claim 119 above, and further in view of Webb et al. (1993, previously cited) and Buck et al. (1998, previously cited).

Myakishev et al., Nuack et al., and Nazarenko et al. teach as noted above.

Regarding claim 98, Nazarenko et al. teach rhodamine (see column 2 line 5) which can be used to label a primer.

With regard to claim 98, Nazarenko et al. disclose amplification of DNA with primers designed for amplification and detection as given above.

Myakishev et al., Nuack et al., and Nazarenko et al. teach primers and probes in general and teach various primer and probe sequences but do not specifically teach SEQ ID NOs: 19 or 25.

Webb et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 19 and 25 of the instant disclosure in Accession no. M60048 (see Table 1 above). It is noted that the instant primer sites of SEQ ID NOs: 19 and 25 are contained within the sequence disclosed by Webb et al.

The above described references of Myakishev et al., Nuack et al., and Nazarenko et al. do not specifically disclose the identical primer sequences of SEQ ID NOs: 19 and 25 primers, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the Accession no. M60048 and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers

are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

18. Claims 142 and 143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Myakishev et al., Nauck et al., Nazarenko et al., Becker et al., and Holland et al. as

applied to claim 136 above, and further in view of Andersson et al. (2001, previously cited) and Chetverin et al. (1993, previously cited).

Myakishev et al., Nauck et al., Nazarenko et al., Becker et al., and Holland et al. do not specifically teach a covalent linker but teach the other limitations of claims 142 and 143 as found above and teach high throughput/multiplex methods (see Nazarenko et al., column 36 lines 3-9).

Regarding claims 142 and 143, Andersson et al. teaches attachment of probes/primers to solid supports (column 11 lines 55 and 56) which can be through a covalent linking moiety (column 11 line 15) and detection through FRET (see column 10 line 22) and where solid phase can be the translucent silica or glass polymers for amplification and detection of 5' end bound target nucleic acids as further taught by Chetverin et al. (see p. 8, 3<sup>rd</sup> paragraph and claims 36, 41, and 144).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Nazarenko et al. by using linkers to solid supports as suggested by Andersson et al. and Chetverin et al. with a reasonable expectation of success. The motivation to do so is provided by Andersson et al. who teach that methods using the covalently bound probes of Chetverin et al. have enhanced sensitivity (column 11 lines 20 and 21). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

**Conclusion**

19. No claim is free of the prior art.
20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples  
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Examiner, Art Unit 1637  
August 3, 2009

/Teresa E Strzelecka/  
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August 4, 2009